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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,816	12/08/2000	Reinhard Ebner	PF470P1	1781

22195 7590 06/10/2002

HUMAN GENOME SCIENCES INC
9410 KEY WEST AVENUE
ROCKVILLE, MD 20850

EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	10

DATE MAILED: 06/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 4/4/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 50-103 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 50-103 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1996-421-632/40206

Part III: Detailed Office Action

Claims 50-103 are pending and under consideration. Applicants traversal of the restriction requirement in paper number 8, filed 4/10/02 is moot as all non-elected claims have been canceled.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are directed.

It is noted that the specification refers to the protein of SEQ ID NO: 4 as Interleukin-22. However, it is noted that, while applicant may be their own lexicographer, the nucleic acid of SEQ ID NO: 3 does not encode the protein which has attained recognition in the art as being Interleukin-22. See enclosed NCBI printout of locus HSA277248, "Homo sapiens IL-22 gene for interleukin 22, exons 1a-5".

The information disclosure statement filed 4/9/02 has been considered. References AH-BX are Genbank Accession numbers and have not been considered, as the relevance of such to the claimed subject matter cannot be assessed in the absence of either a statement or relevance or an alignment to SEQ ID NO: 4.

Objections and Rejections under 35 U.S.C. §§101 and 112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 50-103 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The instant application discloses a portion of a protein which applicants designate Interleukin 22 (IL-22) and a nucleic acid which encodes such, SEQ ID NO: 3. The specification states at page

14 that the cDNA was isolated from a epileptic frontal cortex cDNA library. At page 71 it is disclosed that the nucleic acid is expressed in bone marrow, skeletal muscle, and brain. At page 14, it is clearly stated that SEQ ID NO: 3 is only a partial open reading frame, that is, that the complete coding sequence is not represented. At pages 14-16 there is a structural analysis of the putative protein, stating that it is related to IL-20 and IL-17 based on similarity in a number of small domains; however, there is no functional significance disclosed for those domains. At page 127, it is disclosed that both IL-21 and IL-22 modulate secretion of IL-6 from NIH-3T3 cells. Because applicants claim the antibodies in terms of the proteins they bind, the utility of the protein can be considered in determining utility of the antibody that binds to it. There is no other specific biological activity disclosed for the protein, however, the specification contains conjecture such that the protein may activate or inhibit proliferation, differentiation or mobilization of immune cells (page 129). At pages 129-137 a number of possible uses for the encoded protein are presented, including treatment of hyperproliferative disorders, infections disease, regeneration of tissue, chemotaxis, and binding. With regard to the claimed antibodies themselves, the specification discloses that such may be used to purify, detect or target the protein to which the antibodies bind (page 77), be used in in vitro and in vivo diagnostic and therapeutic methods or to quantitate protein (page 80), may competitively inhibit binding of the protein to its receptor or of other antibodies to the protein, may have agonist or antagonist activity (page 79). The specification also discloses the use of the claimed antibodies for "immunophenotyping", i.e. as a cell- or development- specific marker. There is no working example in which any biological activity is demonstrated for the protein, no cellular or developmental expression patterns are disclosed, nor is any use exemplified for the claimed antibodies.

None of the aforementioned uses is considered to be specific, substantial and credible, as set forth in the Utility Examination Guidelines of 1/5/2001, Federal Register 66(4) beginning at page 1092. It is not predictable that IL-22 will share function with other interleukins, nor if so, what functions would be shared. The assertion that the disclosed IL-22 would have biological activities as set forth above cannot be accepted in the absence of supporting evidence, because the proposed

activities of the protein or other uses of the claimed nucleic acid are merely conjectural, and the specification 'discloses' numerous mutually exclusive activities or uses, such that none can be considered to be credible without any supporting evidence. Further, the relevant literature indicates that prediction of function from structure is not accurate, and reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities, such that the scattered similarities to other known interleukins cannot be taken to be predictive of any particular function. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural

similarity due to evolution from a common ancestral gene. Accordingly, in view of the cited art, the skilled artisan would not accept, without experimental confirmation, that IL-22 would have any particular of the plethora of proposed activities.

With regard to the remaining uses asserted by applicants, the disclosed use for diagnosis, treatment or prevention of a disease cannot be considered to be specific or substantial, much less credible, as there is no disclosure of any disease or condition which could be so diagnosed or treated. Use for "immunophenotyping" is not considered by the Patent Office to be a specific or substantial utility, as such use could be asserted for *any* naturally occurring protein, and further because there has been no characterization of the expression of the disclosed IL-22. The disclosure that the encoded protein may modulate immune system cell proliferation and differentiation in a dose-dependent manner is merely an invitation to experiment, and would not be considered credible by one of skill in the art; mere homology and expression patterns is not accepted by those of skill in the art as being predictive of function, and the term "modulate" can encompass either a positive or negative effect. Finally, although there is a clear statement that the protein to which the claimed antibodies bind modulates secretion of IL-6 from NIH-3T3 cells, this does not satisfy the utility requirement because it is not clear whether this is positive or negative modulation nor under what conditions such occurs, and because it is not clear what utility such an effect would convey. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to antibodies which bind a protein which has undetermined function or biological significance, and cells which produce such. Until some actual and specific activity can be attributed to the protein

identified in the specification as IL-22 protein or the antibodies that bind to it, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-103 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 77-103 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R.§1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC209665 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that all restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. See 37 C.F.R.§1.808(a)(2).

Claims 51, 67, and 77-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims which recite that the protein to which the claimed antibodies bind is glycosylated, e.g. claims 51, 67, 78, and 94 are not supported by the specification because there is no description of any glycoslyation of the protein represented by SEQ ID NO: 4 residues 1-160. While it is possible that the protein is glycosylated, there is no description of such. It is not predictable where or how a protein will be glycosylated, and in what host cell systems such glycosylation will occur. While it is possible that glycosylation can affect the immunogenicity of a protein, such is also not predictable. Therefore, with respect to antibodies that would bind specifically to a glycosylated form of the protein (as opposed to a non-glycosylated form of the protein) there is no written description of such glycosylation, and therefore of the antibodies that would bind to such. A mere conjecture that the protein might be glycosylated under some unspecified conditions is not sufficient to describe antibodies that bind to such a glycosylated protein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the unmodified protein of SEQ ID NO: 4, the skilled artisan cannot envision the detailed chemical structure of the glycosylated protein, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only antibodies which bind to the unmodified protein of SEQ ID NO: 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims drawn to antibodies which bind a protein encoded by a deposited plasmid, i.e. claims 77-103, also lack adequate written description. At page 9, paragraph 1 of the specification, it is stated that "a representative clone containing all or most" ... "of the sequence for SEQ ID NO: 3 was deposited". It is not clear what has been deposited, of what it encodes. "All or most" is not an adequate written description of the deposited material.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51, 57, 58, 63-65, 67, 72, 73, 78 84, 85, 90-92, and 94-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 51, 67, 78 and 94 are indefinite because it is not clear how the glycosylation state of the protein affects the claimed antibodies, both because it is not predictable that glycosylation will change the antigenic structure of the protein, and because there is no written description of such glycosylation, such that the metes and bounds of the claims cannot be determined.

Claims 57, 58, 72, 73, 84, 85, 99 and 100 are indefinite as it is not clear how the recitation that the antibody can be used in a particular assay further limits the claimed antibody; the person of ordinary skill in the art would reasonably expect any antibody of the claims from which these claims depend to be so usable.

Claims 63 and 90 are grammatically incorrect and therefore indefinite. As written, the modifier "obtained from an animal" is misplaced, such that the claimed fragment must be obtained

from an animal. The claims should be amended to read "An isolated antibody obtained from an animal that has been immunized..., or a fragment of said antibody, wherein said antibody or fragment thereof..." to be remedial.

Claims to assay methods, i.e. claims 61, 62, 76, 88-89 and 103, are incomplete. To use claim 61 as an example, the claim as written is a "method of detecting", by "detecting", which is not a method step. The claims should be amended to indicate that the result of step (a) is the formation of a complex, and detection of that complex indicates that IL-22 protein is present. Further, the claims fail to further limit the claims from which they depend, as an assay method does not further limit an antibody.

The remaining claims are rejected for depending from an indefinite claim.

Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50, 51, 53-58, 61-65, 67, 77, 78, 80-85, 88, 89, 90, 92, 94, 96-100 and 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Sutcliffe, U.S. Patent Number 5,242,798.

Sutcliffe discloses a synthetic peptide having 13 amino acids, 6 of which match SEQ ID NO: 4 at residues 47-52 (RSVSPW); see "P2" at column 17, penultimate line, and claims.. The peptides are disclosed for use in making antibodies (abstract) and in immunoassays for proteins to which the antibodies bind, meeting the limitations of the assay claims, see col. 35. See col. 16 at lines 24-27 which discloses that antibodies were raised in rabbits (an animal) and reacted strongly "with the appropriate polynucleotides by ELISA" the person of ordinary skill in the art would also expect the same antibodies to bind in a Western blot. At column 2, Sutcliffe discloses that the "idiotype-

containing polyamide portion of an antibody" may be used; this is an Fab fragment, which meets the limitation of claims such as claim 54. Pharmaceutical compositions are also disclosed, and at column 7, Sutcliffe teaches that the peptide to which the antibodies are raised may be a glycosylated derivative, see line 68. As approximately half of Sutcliffe's P2 is made up of sequence found in SEQ ID NO: 4, it would be expected that antibodies to P2 would bind to a protein having SEQ ID NO: 4. Accordingly, the claims, taken as a whole, are anticipated by the disclosure of Sutcliffe. In making this rejection, the Examiner is presuming that the deposited strain encodes SEQ ID NO: 4, however, see rejections under 35 U.S.C. § 112, above.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 59, 60, 66-67, 69-76, 86, 87, 91, 93, 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sutcliffe, U.S. Patent Number 5,242,798 in view of Coughlin, U.S. Patent

Number 5,256,766.

The claims differ from those rejected under 35 U.S.C. § 102(b) above in that they recite that the antibody is a monoclonal antibody, or that the claimed matter is a cell or hybridoma that produces such an antibody.

The teachings of Sutcliffe are summarized above. Sutcliffe does not teach a monoclonal antibody, or a cell or hybridoma that produces such an antibody.

The production of monoclonal antibodies and cells that make them is notoriously old in the art. For example, Coughlin teaches recombinant thrombin receptor and antibodies thereto. Columns 11-12 teach the production of polyclonal and monoclonal antibodies, including hybridoma cells producing the monoclonal antibodies. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make hybridoma cells and monoclonal antibodies as taught by Coughlin reactive with the P2 peptide of Sutcliffe. The person of ordinary skill in the art would have been motivated to do so to attain the known and expected advantages of monoclonal antibodies, viz. ease of production and purification.

Claims 50-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonaldo et al., locus HUMNOTIA in view of Sibson et al., WO94/01548.

Locus HUMNOTIA is 99.2% identical to bases 21-276 of SEQ ID NO: 3, which encodes residues 7-92 of SEQ ID NO: 4. The primary reference does not specifically disclose recombinant expression of the protein encoded by the disclosed cDNA, nor the production of antibodies thereto.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA's disclosed as Locus HUMNOTIA to express the encoded polypeptide and then make antibodies thereto as taught by Sibson et al. in view of Sibson et al.'s suggestion that

it would be desirable to do so, as cited above. It would further have been obvious to use such antibodies in a detection assay consistent with, for example, claim 61, as Sibson teaches the use of such antibodies to detect proteins to which they bind. The production of polyclonal, chimeric, single chain, and labeled antibodies, as well as of hybridoma cells that produce antibodies is further considered obvious over Bonaldo et al. in view of Sibson et al., as all are notoriously old and well known in the art, and would be immediately envisaged by the person of ordinary skill in the art upon reading the Sibson et al. disclosure. With respect to claims 77-103, the Examiner presumes that the deposited clone encodes all or a portion of SEQ ID NO: 4.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

WO/00/15798, Presnell et al., cited by applicants, discloses a protein designated zTGF beta-9, the coding sequence for which is 99.8% identical to bases 21-1642 of SEQ ID NO: 3.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Spector via telephone number 703-746-5228. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

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